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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/306,986	05/07/1999	THUAN QUOC TRINH	0942.4570001	4261

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EXAMINER
HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
1652	27

DATE MAILED: 08/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/306,986	TRINH ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-13,56 and 70-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-13,56 and 70-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/11/2003 has been entered.

Applicants amendment of claims 57-69 and amendment of claim 8, Paper No. 26, is acknowledged. Claims 8-13, 56 and 70-75 are at issue and are present for examination.

Applicants' arguments filed on 6/11/2003, Paper No. 26, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-13, 56 and 70-75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 (9-13, 56 and 70-75) are indefinite in the recitation "incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said double-stranded DNA and sufficient to degrade single-stranded RNA." While this recitation is not in and of itself indefinite, in light of applicants arguments in response to the previous art rejections, this recitation is indefinite. Applicants in their response to the previous art rejections (i. e. 102 rejections over Davey et al. and Kenten et al.) state that neither of the references satisfy the limitation of part b) of claim 8 because neither of these references teach the degradation of single stranded RNA. As was stated below and previously, the current recited limitation does not necessitiate that single-stranded RNA be degraded, but rather it states that merely the mixture be incubated in conditions "**sufficient to degrade**" single-stranded RNA. As stated previously, the single-stranded RNA need not be degraded, but merely the conditions be such that it could be degraded. In support of applicants previous arguments in response to the previous art rejections, applicants point out that the references cited used RNase H, and applicants suggest that RNase H cannot degrade single-stranded RNA, yet in claim 9, which depends from claim 8, applicants specifically limit the ribonuclease of the invention to a number of ribonucleases including RNase H. This therefore results in some confusion. Can Rnase H be used in the invention or not?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 8, 9, 10, 13 and 71-73 are rejected under 35 U.S.C. 102(b) as being anticipated by Davey et al. (U.S. Patent No: 5,409,818, issued 4/25/1995).

The rejection is stated in the previous office action as it applies to claims 8, 9, 10, 13 and 71-73. In response to this rejection applicants have amended claim 8 and traverse the rejection as it applies to the amended claims. It is noted that applicants amendment does not effect the rejection. Applicants traverse the rejection on the basis that "A claimed invention is anticipated under 35 U.S.C. 102 only if there is disclosure in a single piece of prior art of each and every limitation of a claimed invention". Applicants submit that Davey does not disclose conditions sufficient to degrade single-stranded RNA and therefore, does not anticipate the present invention. Applicants recite a portion of the previous rejection in which it was stated:

> "Davey et al. teach a nucleic acid amplification process which involves the synthesis of RNA and double stranded DNA in a single reaction medium containing reagents comprising multiple DNA polymerases and ribonuclease and incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule and sufficient to degrade single-stranded RNA."

Applicants disagree with this earlier assertion, as applicants submit that the conditions disclosed by Davey are not sufficient to degrade single-stranded RNA. In support of applicants position applicants submit that the ribonuclease used by Davey is "specific for RNA-DNA hybrids" (Davey, column 5, lines 34-35) and that Davey states that "each enzyme or enzyme preparation should be free of deleterious ribonuclease ("Rnase") activities, with the exception of the preferred addition of a ribonuclease activity which is specific for hybrids of RNA and DNA (for example ribonuclease H)." (Davey column 7, lines 17-22). Thus applicants submit that Davey does not teach conditions sufficient to degrade single-stranded RNA.

Applicants argument is not found persuasive because contrary to applicants submissions, the office believes that while Davey et al. may not have intended to or accomplished the "degradation of single-stranded RNA", Davey et al. does teach conditions sufficient to degrade single-stranded RNA. In order to anticipate the rejected claims it is unnecessary for any single stranded RNA to actually be degraded, merely as pointed out by applicants above, "A claimed invention is anticipated under 35 U.S.C. 102 only if there is disclosure in a single piece of prior art of each and every limitation of a claimed invention". No where in applicants claimed method is there a limitation that single-stranded RNA must be degraded. Applicant is reminded that currently rejected claim 8 is drawn to a method which comprises mixing a preparation comprising RNA and double-stranded DNA with one or more DNA polymerases and one or more polypeptides having ribonuclease activity and **incubating** said mixture under conditions **"sufficient to** synthesize a nucleic acid molecule and **sufficient to** degrade single-

stranded RNA". Applicants is reminded that the conditions taught by Davey et al., those conditions that they incubated the taught mixture in are **"sufficient to** synthesize a nucleic acid molecule and **sufficient to** degrade single-stranded RNA", in spite of whether any nucleic acid molecule was synthesized or any single-stranded RNA was degraded.

Further applicants are reminded that claim 9 which depends from claim 8 specifically lists Rnase H as one of the possible examples of ribonuclease activity applicants believe are encompassed by applicants claimed method. As pointed out by applicants above, this is the same ribonuclease activity used in the method taught by Davey et al.

Thus claims 8, 9, 10, 13 and 71-73, remain anticipated by Davey et al.

Claims 8, 9, 10, 13, and 72 are rejected under 35 U.S.C. 102(e) as being anticipated by Kenten et al. (U.S. Patent No: 6,048,687, filed 6/7/1995).

The rejection is stated in the previous office actions as it applies to claims 8, 9, 10, 13 and 71-73. In response to this rejection applicants have amended claim 8 and traverse the rejection as it applies to the amended claims. It is noted that applicants amendment does not effect the rejection. Applicants traverse the rejection as the above rejection over Davey et al. on the basis that in order to anticipate claim 8, the taught method requires conditions sufficient to degrade single-stranded RNA. As above, applicants submit that Kenten does not disclose conditions sufficient to degrade single-

stranded RNA and therefore does not anticipate the present invention. As above, applicants recite a portion of the previous rejection in which it was stated:

> "the preparation taught by Kenten et al. comprises RNA and double-stranded DNA. It is noted that Kenten et al. teach the addition of a ribonuclease, and this is encompassed by claim 9 drawn to a number of specific ribonucleases, as well as fragments, variants derivatives or mutants thereof."

Aa above, applicants disagree with this earlier assertion, as applicants submit that the conditions disclosed by Kenten are not sufficient to degrade single-stranded RNA. In support of applicants position applicants submit that the ribonuclease used by Kenten "hydrolyses RNA of an RNA-DNA hybrid without hydrolyzing single or double-stranded RNA or DNA." (Kenten, column 4, lines 20-22) and that Kenten refers to several publications for a detailed description of the amplification process used (Kenten column 2, line 66, to column 3, line 4). Applicants point out that one of these references is the European equivalent of the Davey patent discussed above, thus the amplification method of Kenten is the same as that of Davey and similarly does not disclose conditions sufficient to dedgrade single stranded RNA. As above applicants argument is not found persuasive, because contrary to applicants assertion Kenten et al. does teach conditions sufficient to degrade single-stranded RNA.

In order to anticipate the rejected claims it is unnecessary for any single stranded RNA to actually be degraded, merely as pointed out by applicants above, "A claimed invention is anticipated under 35 U.S.C. 102 only if there is disclosure in a single piece of prior art of each and every limitation of a claimed invention". No where in applicants claimed method is there a limitation that single-stranded RNA must be degraded.

Applicant is reminded that currently rejected claim 8 is drawn to a method which comprises mixing a preparation comprising RNA and double-stranded DNA with one or more DNA polymerases and one or more polypeptides having ribonuclease activity and **incubating** said mixture under conditions **"sufficient to** synthesize a nucleic acid molecule and **sufficient to** degrade single-stranded RNA". Applicants is reminded that the conditions taught by Davey et al., those conditions that they incubated the taught mixture in are **"sufficient to** synthesize a nucleic acid molecule and **sufficient to** degrade single-stranded RNA", in spite of whether any nucleic acid molecule was synthesized or any single-stranded RNA was degraded.

Further applicants are reminded that claim 9 which depends from claim 8 specifically lists Rnase H as one of the possible examples of ribonuclease activity applicants believe are encompassed by applicants claimed method. As pointed out by applicants above, this is the same ribonuclease activity used in the method taught by Kenten et al.

Thus claims 8, 9, 10, 13 and 72, remain anticipated by Kenten et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 70, 74 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davey et al. et al. (U.S. Patent No: 5,409,818, issued 4/25/1995).

The rejection is stated in the previous office action as it applies to claims 70, 74 and 75. In response to this rejection applicants have amended claim 8, from which claims 70, 74 and 75 depend, and traverse the rejection as it applies to the amended claims. It is noted that applicants amendment does not effect the rejection.

Applicants traverse the rejection on the basis that applicants submit that the office has failed to establish a *prima facie* case for obviousness of the presently claimed invention. As above applicants submit that Davey does not disclose conditions sufficient to degrade single-stranded RNA and there is no suggestion in Davey to modify the conditions in order to make them sufficient to degrade single-stranded RNA. This argument is not found persuasive for the same reasons discussed above, that Davey et al. in fact does disclose conditions sufficient to degrade single-stranded RNA. As above, Applicant is reminded that currently rejected claim 8 is drawn to a method which comprises mixing a preparation comprising RNA and double-stranded DNA with one or more DNA polymerases and one or more polypeptides having ribonuclease activity and **incubating** said mixture under conditions **"sufficient to** synthesize a nucleic acid molecule and **sufficient to** degrade single-stranded RNA". Applicant is reminded that the conditions taught by Davey et al., those conditions that they incubated the taught mixture in are **"sufficient to** synthesize a nucleic acid molecule and **sufficient to** degrade single-stranded RNA", in spite of whether any nucleic acid molecule was synthesized or any single-stranded RNA was degraded.

Claims 8-12, 70, 71 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Major (Biotechniques, Vol 12, No. 1, 1992, pages 40-43) and Maudru et al. (Journal of Virological Methods 66: 247-261, July 1997).

The rejection is stated in the previous office action as it applies to claims 70, 74 and 75. In response to this rejection applicants have amended claim 8, from which claims 70, 74 and 75 depend, and traverse the rejection as it applies to the amended claims. It is noted that applicants amendment does not effect the rejection.

Applicants traverse the rejection on the basis that the Examiner has mis-characterized the teachings of Maudru and that Maudru does not stand for the proposition that "background signals of PCR based nucleic acid synthesis reactions is due to an intrinisic RNA-dependent DNA polymerase activity of *Taq* DNA polymerase". Applicants submit that Madru is concerned with eliminating background reverse transcriptase activity in a PCR-based reverse transcriptase activity. Applicants follow this assertion by a somewhat confusing characterization of the protocol of Madru (see page 15, lines 3-16), followed by the statement that "One of skill in the art, reading Madru as a whole, would conclude that Madru stands for the proposition that background reverse transcriptase activity can be eliminated in a reverse transcriptase assay by the degradation of template RNA prior to amplification" (Madru page 258, section 4, second sentence.)

Applicants argument is not found persuasive because it is believed that applicants have mischaracterized the teachings of Madru et al. First, with respect to

applicants comments that "Maudru does not stand for the proposition that 'background signals of PCR based nucleic acid synthesis reactions is due to an intrinisic RNA-dependent DNA polymerase activity of *Taq* DNA polymerase'", applicants attention is directed to the the abstract of Madru , which states "The background signal of the PBRT assay was found to be due to an intrinisic RNA-dependent DNA polymerase activity of the Taq DNA polymerase, the enzyme used for the PCR." This statement, repeated verbatim from the abstract of Maudru et al. is interpreted exactly as was previously stated in the original rejection, Maudru et al. teach that the background signal of the PCR-based reverse transcriptase assay is due to an intrinisic RNA-dependent DNA polymerase activity of the *Taq* DNA polymerase. While applicants may take from the teachings of Maudru et al. additional information, applicants assertions that this referred to interpretation is incorrect is not found persuasive.

Second, with respect to applicants comments regarding "that one of skill in the art, reading Madru as a whole, would conclude that Madru stands for the proposition that background reverse transcriptase activity can be eliminated in a reverse transcriptase assay by the degradation of template RNA prior to amplification" (Madru page 258, section 4, second sentence.), applicants are directed to the actual sentence that applicants refer to here which states: The use of thermostable DNA polymerases that have low RNA-dependent DNA polymerase activity and the inclusion of an Rnase incubation prior to the PCR amplivfication of the cDNA product effectively eliminated the background of the assay", (i.e. the generation of background cDNAs). This statement

supports this original rejection completely as originally presented, that is the inclusion of a Rnase along with *Taq* polymerase to remove residual background as a result of RNA.

Finally, applicants further assert that one of skill in the art would have had no motivation to add Rnase to the PCR amplification reaction of Major since there is no suggestion that RNA or reverse transcriptase has anything to do with the assay described in Major.

This is also not found persuasive because as previously stated, one of ordinary skill in the art at the time of filing would have been motivated to add a polypeptide with ribonuclease activity to the method taught by Major, in order to remove residual RNA sequence contamination from the targeted nucleic acid template, in any preparation which would contain substantial amounts of background RNA, such as a bacterial colony lysate, in order to decrease the level of background signal from the taught PCR assay. As the ordinary artisan would know that **any nucleic acid preparation that has not been purified, such as a bacterial colony lysate, contains substantial amounts of contaminating RNA**, the motivation for the removal of these contaminating sequences is that this would increase the sensitivity of the taught PCR assay method from bacterial colony lysates, thus eliminating the need for purification of the template DNA and reducing the time and work needed to perform the assay This is supported by both Major, who teach that some primer sets when used with bacterial colony lysates result in extra minor bands, and Maudru et al. who teach that the background signals of PCR based nucleic acid synthesis reactions is due to an intrinsic RNA-dependent DNA polymerase activity of *Taq* DNA polymerase. The reasonable expectation of success

for the inclusion of ribonuclease in the nucleic acid synthesis reaction of Major comes from the high degree of knowledge in the field of nucleic acid synthesis and the results of Maudru et al. who teach that the simultaneous addition of ribonuclease in order to eliminate background signals in the polymerase chain reaction mix containing *Taq* DNA polymerase did not adversely affect the synthesis of the desired nucleic acid products by PCR.

Thus claims 8-12, 70, 71 and 73 remain obvious by Major and Maudru et al.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard G Hutson, Ph.D.

Primary Examiner
Art Unit 1652

rgh